REMARKS

Following entry of the foregoing amendments, claims 38, 40, and 61 will be pending in this patent application. Claims 38 and 40 have been amended, and claims 1 and 58 have been canceled, herein, without prejudice. New claim 61 has been added. Support for the amendments and new claim is found throughout the specification as originally filed, including, for example, experimental example 6 at pages 84 to 86, and the amendments and new claim thus do not introduce new matter into the application.

Applicant respectfully requests reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

Alleged Obviousness

Claims 1, 38, 40, and 58 have been rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by published U.S. patent application number 2003/143732 ("the Fosnaugh application") in view of published U.S. patent application number 2003/0166282 ("the Brown application"), and have been independently rejected as allegedly rendered obvious by the Fonsaugh application in view of published U.S. patent application number 2005/0181382 ("the Zamore application"). If the Office considers these rejections to apply to the claims as amended herein, applicant respectfully requests reconsideration and withdrawal thereof because the presently claimed compositions would not have been obvious before applicant's invention in view of the cited references.

New claim 61 recites compositions comprising a duplex consisting of an antisense oligonucleotide and a sense oligonucleotide in which the antisense and sense oligonucleotides are complementary to each other and the antisense oligonucleotide is complementary to a target nucleic acid. Each nucleoside of the antisense oligonucleotide comprises a 2'-fluoro modification, each guanine of the sense oligonucleotide is substituted with an inosine, and the sense oligonucleotide comprises at least one inosine.

The claimed compositions would not have been obvious before applicant's invention in view of the description provided in the cited references because the references provide no reason to design oligomeric compounds having the particular pattern of chemical modifications presently claimed in light of the fact that there would have been no basis before

applicant's invention for those skilled in the art to reasonably expect that the claimed oligomeric compounds would have had the desired activity of inhibiting target mRNA expression.

The Fosnough, Brown, and Zamore applications, when considered individually or in combination, merely describe a vast number of chemical modifications that could be incorporated into RNA in a nearly infinite number of possible combinations. Nothing in the references suggests selecting the particular chemical modifications presently claimed or combining the modifications in the specific manner claimed. The claimed pattern of chemical modifications thus would not have been obvious to try before applicant's invention. Moreover, even if the claimed chemical modifications would have been obvious to try, the art was so unpredictable that there would not have been a reasonable expectation that oligomeric compounds bearing the claimed pattern of modifications would have exhibited the desired biological activity. The Office correctly summarizes applicant's reasoning in this regard, noting that "the combination of references is unpredictable because one would not know *a priori* if the claimed combination is going to have enhanced properties relative to unmodified compounds."[1] If it would have been obvious to try the claimed combination of chemical modifications, which applicant does not concede, the claimed oligomeric compounds would still have been nonobvious, because there would not have been a reasonable expectation that the compounds would have successfully exhibited the desired biological activity. The claimed oligomeric compounds would therefore not have been obvious before applicant's invention.

The Office dismissed applicant's arguments presented in the reply filed April 3, 2008 regarding the nonobviousness of the claimed oligomeric compounds by improperly shifting the burden of proof required to establish *prima facie* obviousness to applicant. Specifically, the Office asserts that "there is no evidence of record to indicate that the choice of the claimed modifications would be more than design choice or that those in the art would expect the claimed modifications not to work, therefore there is no reason to consider the results observed in the working examples as unexpected."[2] The Office appears to confuse

[1] Office action dated July 2, 2008, page 8.
[2] *Id.*

unexpected results with unpredictability in the art and to improperly shift the burden for establishing *prima facie* obviousness to applicant.

Once *prima facie* obviousness has been established, the burden is shifted to applicant to show nonobviousness through secondary considerations, one of which is unexpected results.[3] In this case, however, *prima facie* obviousness has not been established, in part because the art was unpredictable and those skilled in the art would not have reasonably expected oligomeric compounds having the claimed combination of chemical modifications to have successfully exhibited the desired biological activity before applicant actually demonstrated such activity. The Office's assertion that there is no evidence of record to show that the those in the art would "expect the claimed modifications not to work" is insufficient to support an assertion of *prima facie* obviousness. It is the *Office's* burden to establish that those of skill in the art would have reasonably expected that oligomeric compounds bearing the claimed combination of chemical modifications would have had the desired biological activity, but *no such showing has been made.*

The cited references merely provide general suggestions for incorporating any of a vast number of chemical modifications into RNA in a dizzying number of possible combinations, some of which may work and many of which likely will not. The Office flatly dismisses the inventive research necessary to design and test such combinations by simply labeling each success as a "design choice." As noted, there is no way to know *a priori* which compounds and combinations will work in this unpredictable field. Applicant thus respectfully submits that the present rejections are based on hindsight, and requests withdrawal thereof.

Alleged Double Patenting

Claims 1, 38, and 40 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1, 5, 9, 11, 79, and 80 of copending U.S. patent application number 10/700,689 ("the 689

[3] "The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness. If, however, the examiner does produce a *prima facie* case, the burden of coming forward with evidence or arguments shifts to the applicant who may submit additional evidence of nonobviousness, such as comparative test data showing that the claimed invention possesses improved propewrties not expected by the prior art." M.P.E.P. § 2142

application") in view of the Brown application. Applicant respectfully requests reconsideration and withdrawal of this rejection for the reasons articulated above with respect to the rejections for alleged obviousness. In addition, applicant notes that the cited claims of the 689 application do not recite inonsine modifications and the Office has not articulated any credible reason why those of skill in the art would have combined the subject matter recited in the cited claims of the 689 application with that of the Brown application to arrive at the presently claimed oligomeric compounds. The Office has not indicated why those skilled in the art would have incorporated the *particular* pattern of chemical modifications claimed into oligomeric compounds and has not provided any evidence that those skilled in the art would have had a reasonable expectation that such oligomeric compounds would have successfully exhibited the desired inhibitory activity towards target mRNA. Applicant accordingly, respectfully, requests withdrawal of the rejection.

Conclusion

Applicant believes that the foregoing constitutes a complete and full response to the official action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,

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